REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

I. Status of the claims

Claims 88-95 are being added. Exemplary support for the new claims may be found, for instance, in Examples 1-4, including Tables 2-5. As the amendments add no new matter, entry and examination thereof is respectfully requested.

This amendment adds claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

After amending the claims as set forth above, claims 1-7, 12, 14-32, 37, 39-46, 67-74, 76-79, 82-83 and 85-95 are now pending in this application.

II. Priority

The Examiner alleges that the priority application U.S. Appl. No. 60/414,097 fails to provide support for the claimed invention. For reasons previously presented, Applicants disagree (see e.g., Reply dated March 22, 2010 at pages 9-11). Regarding newly added claims 88-95, Applicants also note that the priority document provides support for storing the recited dried particles "for at least 7 days before delivery from a particle-mediated delivery device." *See* U.S. Appl. No. 60/414,097 at Example 1, Experiment B, and Example 2, on pages 30-32. Thus, Applicants submit that the priority application, by disclosing methods for making and storing the recited compositions, as well as the unexpected stability of such compositions, supports the presently pending claims.

III. Claim rejections – 35 U.S.C. § 112, first paragraph - "New Matter"

Claims 1-7, 12, 14-32, 37, 39-46, 67-74, 76-79, 82, 83 and 85-87 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly introducing new matter. Specifically, the Examiner asserts that these claims "contain subject matter which was not described in the specification ins such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention...as modified by the new claimed scope." Office Action at page 5. Applicants respectfully traverse this ground for rejection.

Any asserted issue relating to "new matter" is necessarily based on the written description requirement of 35 U.S.C. § 112, 1st ¶. As stated in a leading case cited in MPEP § 2163.06 as related to issues of new matter, "that a claim may be broader than the specific embodiment disclosed in a specification is in itself of no moment." *In re Rasmussen*, 650 F.2d 1212, 1215 (CCPA 1981). Likewise, "[b]roadening a claim does not add new matter to the disclosure. Disclosure is that which is taught, not that which is claimed. An applicant is entitled to claims as broad as the prior art and his disclosure will allow." *Id.* at 1214.

In this case, the specification clearly discloses and describes the subject matter of all pending claims at issue. Assertions by the Examiner (Office Action mailed June 16, 2010, page 7) that Applicants "excluded" or "carved out" certain embodiment disclosed in Table 2 "to obtain the maximum coverage, while overcoming rejections of record" is irrelevant to a written description analysis. The Examiner's assertion (*id.*) that "post-filing analysis is necessarily one of obviousness" is similarly irrelevant, not to mention confusing because it combines multiple areas of law. The proper inquiry in a written description assessment is whether Applicant's specification conveys "with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the [claimed] invention." *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991).

The present application clearly discloses particles suitable for delivery from a particle-mediated delivery device, and methods for making the same. *See* abstract. As noted in the Summary of the Invention, Applicants "found that nucleic acids can be stably attached to inert metal carrier particles in the presence of a nucleic acid condensing agent and a metal ion chelating agent." Specification at page 3, lines 26-28 (emphasis added). In certain disclosed embodiments, the condensing agent is a homopolymer of arginine of the formula $(Arg)_x$, wherein x is from 2 to 10. Specification at page 16, lines 27-30, continuing to page 17, lines 1-2. In other disclosed embodiments, possible chelating agents include EDTA, DTPA and desferal (DFO). Specification at page 18, lines 8-17. In other disclosed embodiments, the nucleic acid is deposited on the inert metal carrier particles in the presence of a sugar, such sucrose, trehalose, lactose, raffinose and/or mannitol. Specification at page 18, lines 18-24. *See also* original claim 21.

Examples in the specification expressly disclose experiments examining the effect of different condensing agents, metal ion chelating agents, sugars and polyarginine peptides on the physical stability of relevant nucleic acid-coated particles. For example, Example 1 (Experiment B) demonstrates that sucrose is better than trehalose, which is better than raffinose, with regard to physical stability of the DNA on particles prepared in the presence of polyarginine peptide. Specification at page 28, lines 11 and 12. Likewise, chelating agent EDTA is better than DTPA, which is better than desferal. Specification at page 28, lines 11 and 13. As it turns out, when one uses spermidine and salt instead of a metal ion chelating agent and a polyarginine peptide (*see* Example 1, Experiment C), raffinose works better than trehalose, which works better than sucrose—i.e., a different result.

Example 2 in the specification discloses stability studies of various nucleic acid-coated particles dried to a powder. Specification at page 29, lines 24-25, continuing to page 30, lines 1-16. Example 2 presents tests of particle stability at 4 °C and 60 °C, and at 0, 7 and 14 day time points. *Id.* Likewise, in Example 3, the specification examines the stability of dried particles, as tested at 4 °C and 60 °C after 8 weeks. Example 4 presents long-term stabilities studies that

again examine different condensing agents, metal ion chelating agents, sugars and polyarginine peptides. The results are presented in Tables 2 and 5, for example.

As shown in Example 4 and Tables 2 and 5, the specification conveys to those skilled in the art that Applicants possessed the particles recited in independent claims 1, 67 and 85. In claim 1, one obtains particles by a method comprising the steps of: (a) depositing a nucleic acid on inert metal carrier particles in the presence of (i) a homopolymer of arginine of the formula $(Arg)_x$, wherein x is from 2 to 10, or a physiologically acceptable salt thereof; (ii) EDTA; and (iii) a sugar; and (b) drying the particles to a powder; wherein the dried particles have a half life of at least 27 days at 40° C. Independent claim 67 similarly recites particles comprising inert metal carrier particles, a nucleic acid, a homopolymer of arginine of the formula (Arg)x, wherein x is from 2 to 10, or a physiologically acceptably salt thereof, and EDTA, wherein the particles are dried to a powder and have a half-life of at least 27 days at 40° C. Independent claim 85 is similar to claim 1, except that (1) the metal ion chelating agent is EDTA, or (2) the sugar comprises sucrose, or both (1) and (2).

Example 4 and Tables 2 and 5 disclose each and every element recited in claims 1, 67 and 85. Multiple examples in the specification (e.g., Example 1, Experiment B, and Example 4) indicate that EDTA is a particularly good metal ion chelating agent (regardless of sugar used) with regard to stability when preparing the dried nucleic acid-coated metal particles as claimed (i.e., using a sugar and a polyarginine peptide). Likewise, the same Examples indicate that sucrose is a particularly good sugar (regardless of metal ion chelating used) with regard to stability when preparing the dried nucleic acid-coated metal particles as claimed.

Table 2 shows that the particles of independent claims 1, 67 and 85 have a half life of at least at least 27 days when stored in a dried powder form at 40° C. *See* TA101.1, TA101.2, and TA101.3 in Table 2 and 3; *see also* Declaration of Dr. Phil White dated March 22, 2010, ¶¶ 8-11. Moreover, Table 5 provides additional support. As discussed below, if relevant particles had a certain half life when stored as a dried powder at 60 °C, skilled artisans would have clearly

understood that such particles undoubtedly had a longer half life when stored at 40 °C, a lower temperature. *See* Tables 2 and 5, indicating that half life increases as storage temperature lowers; *see* results for TA201.5, TA201.15 and TA201.11 at 60 °C in Table 5 (*see also* Table 4).

Thus, Applicants clearly possessed the particles recited in independent claims 1, 67 and 85. *See* Declaration of Dr. Phil White dated March 22, 2010, ¶¶ 8-11. As noted above regarding relevant case law, "that a claim may be broader than the specific embodiment disclosed in a specification is in itself of no moment." *In re Rasmussen*, 650 F.2d 1212, 1215 (CCPA 1981); *see also Union Oil Co. of Cal. v. Atl. Richfield Co.*, 208 F.3d 989, 997 (Fed. Cir. 2000) ("The written description requirement does not require the applicant 'to describe exactly the subject matter claimed, [instead] the description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.'") (citation omitted).

A. Newly added claims 88-95

In the RCE application filed herein, Applicants also add new claims 88-95. As discussed above, the specification clearly discloses that Applicants prepared relevant nucleic acid-coated particles that were unexpectedly stable, even when stored at 40 °C or 60 °C. *See* Examples 2-4. As one can see from data presented in Example 4, such as in Tables 2 and 5 for instance, stability of particles decreases as storage temperature increases from 4 °C to 60 °C. In other words, if relevant particles were stable for at least a certain amount of time when stored at 60 °C, they were undoubtedly stable for even longer periods of time at lower temperatures. As it turns out, the specification presents studies examining the stability of dried particles stored at 4 °C, 25 °C, 40 °C and 60 °C. *See* Examples 2-4, e.g., Tables 2 and 5 in Example 4. Those skilled in the art clearly understood that these studies examined and established stability of relevant dried particles after storage for at least 7 days, at least 14 days, and at least 8 weeks at temperatures ranging from at least 4 °C to at least 60 °C. *See* Examples 2-4, such as Table 2 and 5. *See also* specification stating that "[c]omparing relative decay rates at higher temperatures indicates relative stability at lower temperatures." Specification at page 35, lines 12-13.

B. Summary of the Interview with respect to alleged "new matter" issues

Previous prosecution efforts concentrated on the "half-life" element in pending claims, which led to complicated and confusing rejections by the Examiner. In an effort to streamline prosecution, Applicants proposed new claims 88-95 to the Examiner by fax on August 19, 2010. These claims recite "storing" or "stored" for certain periods of time (at least 7 days or more), instead of "a half life of at least 27 days at 40° C."

In response to this fax, a telephonic interview between the Examiner and Applicants' representative followed on September 7, 2010. In short, the Examiner rebuffed all attempts to obtain any allowable subject matter, such as any independent claim incorporating any limitation of the Examiner's choosing, such as those recited in various dependent claims or otherwise. To obtain consideration of proposed claims, the Examiner indicate Applicants must file a new RCE application, a time consuming and costly enterprise.

The Summary of the Interview presents an accurate presentation the positions of Applicants and the Examiner, including the odd statement by the Examiner that "the step of 'powder' dry was likely infringed by a precipitate in ethanol." Applicants note that pending claims relate to relevant particles dried to a powder, and/or storing dried particles. To make this point abundantly clear, Applicants recite in new claim 88 the step (iii) of "storing the dried particles as a powder for at least 7 days ...," as well as similar language to new composition claim 94. As suggested by the Examiner during the recent telephonic interview, Applicants also recite "wherein the particles are particles suitable for delivery from a particle-mediated delivery device" in the body of new claim 88.

As noted in the Summary of the Interview mailed on September 9, 2010, the Examiner indicated during the interview that "claims to the particles would likely never be allowable" regardless of any recited limitation, i.e., no matter how narrowly the claims are drafted. In this capacity, the Examiner also indicates that "the composition is the composition, and its structure was not modified by having once been stored" with regard to new composition claims 94 and 95.

Applicants note that claims 94 and 95 correspond to particles that are stored as a dried powder for at least seven days. To the extend the Examiner implies that such storage is irrelevant in a prior art analysis, Applicants point out that claims 94 and 95 will not encompass particles that are not stored dried for at least seven days. As discussed in more detail below, the storage element is certainly relevant in a prior art analysis, precisely because the prior art fails to disclose or suggest any DNA-coated particles (regardless of how they are made or what they comprise) that are stored for at least seven days.

During the interview and in the Summary of the Interview, the Examiner again attempted to raise written description issues as relating to new claims 88-95. Once again, this line of reasoning has no basis in light of the clear disclosure in the specification. As presented in Examples 2-4, the specification plainly presents a process for preparing and storing the recited particles, drying the particles to a powder, and then storing the particles for at least 7 days, 14 days, or 8 weeks. Tables 2 and 5 in Example 4 present nucleic acid-coated inert metal carrier particles comprising (a) a homopolymer of arginine of the formula $(Arg)_x$, wherein x is from 2 to 10, or a physiologically acceptable salt thereof; (b) EDTA or DTPA; and (c) a sugar. *See, e.g.*, TA101.1, TA101.2, TA101.3 and TA101.4 in Table 2 and 3; TA201.5, TA201.15 and TA201.11 in Tables 4 and 5. As indicated in the specification, when Applicants conducted long-term stability studies assessing half life (via biological activity in mice and expression studies), Applicants plainly stored relevant particles as a dried powder for at least 7 days, at least 14 days and at least 8 weeks (56 days). *See also* Examples 2 and 3 for express written description support for storage at these specific time frames exactly.

In the Summary of the Interview, the Examiner also suggests that "storage at absolute zero and a million degrees would likely provide enablement/art issues." As discussed in more detail below, no cited prior art discloses or suggests any nucleic-acid coated particle suitable for delivery from a particle-mediated delivery device that is stored for at least 7 days. Applicants also note that dependent claim 89 recites storage at "a temperature in the range of about 4 °C to about 60 °C for at least 7 days before delivery from a particle-mediated delivery device."

Without acquiescing to any possible enablement assertion regarding new independent claims 88 and 94 as presented herein, Applicants respectfully request that the Examiner consider whether he would allow claims 88 and 94 and other dependent claims if independent claims 88 and 94 also recited the temperature range element presented in dependent claim 89.

IV. Claim rejections – 35 U.S.C. § 103

Four different rejections under 35 U.S.C. § 103(a) were presented in the June 16, 2010 Office Action. In each of the rejections, four primary references were asserted: Sanford (U.S. Pat. No. 5,204,253), Balhorn (*Mol. Reprod. Dev.*, (2000) 56: 230-34), Oard (*Plant Cell. Tiss. and Org. Cult.*, (1993) 33(3): 247-50), and Chee (U.S. Pat. No. 6,641,553). Thirteen additional references were cited by the Examiner to allegedly render obvious various aspects of the dependent claims. Applicants respectfully traverse each of these grounds for rejections. The combination of the primary references does not render the pending claims obvious, and none of the additional references cures this deficiency.

A. The primary references do not render the pending claims obvious

In the Office Action mailed June 16, 2010, the Examiner asserted that then pending claims were obvious over Sanford and Balhorn, as evidenced by Oard, and further in view of Chee.

As disclosed in the specification, Applicants prepared nucleic acid-coated particles that were unexpectedly stable, even when stored at temperatures as high as 40°C or 60°C. Through a number of experiments presented for the first time in the instant specification, Applicants discovered a method for preparing and storing relevant nucleic acid-coated metal inert carrier particles, namely one involving the use of (a) a homopolymer of arginine of the formula $(Arg)_x$, wherein x is from 2 to 10, or a physiologically acceptable salt thereof; (b) a metal ion chelating agent; and (c) a sugar, and storing such particles as a dried powder. Likewise, Applicants taught

for the first time storage of such nucleic acid-coated metal carrier particles for at least 7 days, as well as stability of the particles upon that storage.

As discussed in previous responses to Office Actions, the art cited by the Examiner does not arrive at the claimed invention (*see e.g.*, Reply dated March 22, 2010 at pages 16-23). Sanford discloses entirely different particles when it presents ballistic delivery of tungsten particles, onto which plasmid DNA is condensed in a buffer containing EDTA in the presence of spermidine/calcium chloride. (*see* col. 15, lines 14-32). Notably, Sanford fails to disclose or suggest storing disclosed particles for any length of time (much less 7 days or more), nor does it address stability of its disclosed particles. In fact, Sanford implies that they used their particles immediately upon preparation, or at most, after brief storage in ethanol (i.e., not as a dried powder). Nothing in this reference suggests particles as claimed by Applicants, the stability of such particles when stored as a dried powder, or that one might be able to store such dried particles for at least 7 days before viable use.

Like Sanford, Oard teaches the use of spermidine $CaCl_2$ to condense DNA onto a microparticle. *See* Oard at 249, 1st col., bottom ¶. Oard, like Sanford, fails to suggest the use of a homopolymer of arginine for this process, but rather states that prior to DNA precipitation, one can rinse microcarriers with poly-L-lysine. *Id.* at 1st col., second from bottom ¶. In this context, Oard states "[t]he use of gold flakes and poly-L-lysine did reduce clumping relative to the tungsten particles, but did not eliminate the problem entirely." *Id.* at 2nd col., 1st paragraph (emphasis added).

Additionally, like Sanford, nothing in Oard suggests Applicants' particles, the stability of such particles when stored as a dried powder, or that one might be able to store such dried particles for at least 7 days before viable use. Rather, Oard expressly teaches away from storing DNA-coated particles for any length of time, much less at least 7 days, because the disclosed "microcarriers" were prepared and used "as soon as possible after precipitation because the amount of clumping increased over time." *Id.* at 2nd col., 1st paragraph.

Regardless of one's scientific assessment of Balhorn, it is clear that Balhorn provides no teaching or suggestion regarding nucleic acid-coated metal inert carrier particles in a dried powder form, nor the storage or stability of the same. As previously explained, one of skill in the art would not have relied upon teachings in Balhorn, which draw conclusions based solely on experiments performed in solution, to design a stable dried particle coated with DNA. Nothing in this reference, nor any other cited by the Examiner, suggests drying nucleic acid-coated particles to a powder. Nothing in Balhorn suggests storing nucleic acid-coated metal inert carrier particles as dried powder for at least 7 days, nor that such a powder might have an unexpected stability of a half life of at least 27 days when stored at 40° C.

Moreover, as explained previously during prosecution (*see, e.g.*, Reply dated July 9, 2009 at pages 16-17), the stability of particles comprising shorter polymers of arginine, as required by the claimed invention, was very surprising in view of what was known in the art, such as evidenced by Adami et al., *J. Pharm. Sci.*, 87:678-683 (1998). Adami taught, for example, that a polymer of 18 lysine monomers protected DNA from both enzymatic and sonicative-induced degradation, while a shorter polymer of 8 lysine failed to protect DNA from degradation when used as a DNA condensation agent. *See, e.g.*, Abstract and first full ¶ of page 682, left column. Because arginine and lysine are a basic amino acids with similar chemical structure and properties, one of skill in the art would have drawn conclusions for arginine based on the lysine data presented in Adami. Upon reading Adami, one of skill in the art would have expected that longer polymers would be required for enhanced stability, when in fact the present invention indicates otherwise.

When citing yet another reference, the Examiner also asserts that Chee discloses that "microprojectile particles are dried for use," presumably referring to col. 12, lines 35 – col. 13, line 11. (Applicants are unclear what Examiner means by the citation to paragraph 22 in Chee in the Office Action, page 13). In any event, even assuming that the concept of using dried DNA-coated particles for bombardment into tissue was understood in the art, this basic concept does not provide the teachings entirely missing from all of the cited references.

Nothing in Chee or in any of the cited prior art references suggests preparing and storing a dried powder of nucleic acid-coated metal inert carrier particles comprising (a) a homopolymer of arginine of the formula $(Arg)_x$, wherein x is from 2 to 10, or a physiologically acceptable salt thereof; (b) a metal ion chelating agent; and (c) a sugar. Nor does any cited prior art reference suggest that such dried particles would be stable (i.e., have a long half life) at temperatures such as 40° C and 60° C., so that they could be stored at these temperatures for at least 7 days (e.g., at least 27 days at 40° C) and still be viable for use upon delivery from a particle mediated delivery device.

In other words, neither the recited storing nor stability aspects are disclosed, suggested or understood in the prior art. The stability of the recited particles (as measured and disclosed in multiple ways in the specification), discovered and disclosed for the first time by Applicants, was an unexpected result. Nothing in the prior art motivated one to store such particles for even a short amount of time, much less 7 days or longer, before using them in a particle-mediated delivery device. To the extent that the Examiner asserts that such unexpected results "is simply an optimization of what is known" (Office Action, pages 16-17), Applicants point out that one can make such arguments to say that any new improvement, and unexpected results resulting therein, always constitutes optimization.

The proper question here is whether one would have been motivated to prepare and store Applicants' recited particles. Especially in light of a complete lack of understanding regarding the unexpected stability of Applicants' dried particles, and an express teaching away in Oard from storing DNA-coated particles for any length of time, much less at least 7 days, those skilled in the art would not have had the requisite motivation.

B. The additional references do not cure the deficiency of the primary references

As discussed above, the skilled artisan would not deem the pending claims obvious in light of Sanford, Balhorn, Oard and Chee; none of these references, alone or in combination, discloses or suggests the dried, stable particles recited in the claims. In an attempt to strengthen and expand the rejection, the Examiner cites numerous additional references and selects components from each in an effort to piece together the elements of the claims. Applicants respectfully assert it is only with impermissible hindsight that the references would be selected and that the various components hypothetically combined. Unlike the Examiner, the skilled artisan would not have the advantage of hindsight and simply would not have been motivated to combine so many references, and then cherry pick specific elements out of many possibilities presented in each of the references. Again, none of the references, alone or in combination, provides sufficient suggestion, guidance or motivation for the skilled artisan to develop the claimed invention.

As noted above, the Examiner cites numerous additional references, all of which go even more astray from the subject matter of nucleic acid-coated metal inert carrier particles. For example the Examiner asserts that Kwok and Livesey teach the use of sucrose to stabilize DNA condensates. As previously noted during prosecution, Kwok teaches the use of sucrose as a lyoprotectant for freeze-dried DNA/poly-lysine condensates. *See* Kwok at Abstract and page 86, left column, last ¶. Kwok does not relate to the precipitation of DNA onto metal carrier particles in the presence of a homopolymer of arginine and a metal ion chelating agent, and provides no evidence or insight into whether sucrose might help enhance stability of the DNA on such dried particles, especially when stored at temperatures above freezing. Likewise, Livesey provides only general disclosure of cryopreservatives, and does not mention inert metal particles, short homopolymers of arginine or chelators. These two references, either alone or in combination with any other cited references, do not motivated anyone to prepare and store Applicants' recited particles.

The Examiner likewise asserts that Barman teaches "that stabilizers such as saccharides may be used in combination to stabilize the nucleic acid protein complexes." Office Action, page 22 (citing Barman, paragraph 24). Barman teaches the use of polymeric microparticles, not inert metal particles, and mentions that stabilizers may be used, with examples including saccharides and cationic peptides. *See* paragraphs 41 and 46. Barman neither discloses nor suggests nucleic acid-coated metal inert carrier particles, much less those comprising short homopolymers of arginine and a metal ion chelating agent, nor the stability or storage of such particles.

Lastly, the Examiner cites "many references" for the concept that sugars, such as trehalose, were known to stabilized proteins. Office Action, page 25. Again, none of these references teach or suggest nucleic acid-coated metal inert carrier particles at all, much less those comprising short homopolymers of arginine, a metal ion chelating agent and a sugar, nor the stability or storage of such particles.

In summary, the cited prior art entirely fails to disclose or suggest Applicants' particles having the stability recited in independent claims 1, 67 and 85, nor any DNA-coated particles (regardless of how they are made or what they comprise) that are stored for at least seven days as recited in independent claims 88 and 94.

Accordingly, the rejections under 35 U.S.C. § 103(a) are without merit, and reconsideration and withdrawal is respectfully requested.

V. Conclusion

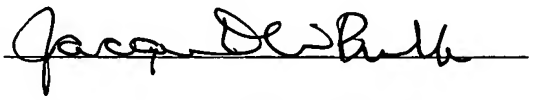
The present application is now in condition for allowance. Favorable reconsideration of the application is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorize payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date: September 16, 2010

By 

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